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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/500,521	SCHREIBER, GIDEON	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *62,66-71,75-82 and 87-94* is/are pending in the application.

4a) Of the above claim(s) *87 and 90-92* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *62, 66-71, 75-82, 88, 89, 93 and 94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date: _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Request for Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 29, 2007 that includes a response to the Advisory action dated October 17, 2006, has been entered. Claims 83 and 85 have been cancelled, and claims 87-94 are newly added. Claims 62, 66-71, 75-82 and 87-94 are pending in the application.

New claims 90 and 91 are directed to non-elected species of the invention and recite methods for augmenting anti-cancer and anti-viral properties of IFNβ, that are not the elected species of multiple sclerosis as an autoimmune disease. Thus, claims 90 and 91 are withdrawn from further consideration. New claims 88 and 89 are examined to the extent that they embrace the elected species of multiple sclerosis as an autoimmune disease and a method of administering to a patient a therapeutically effective amount of a composition comprising the polypeptide of SEQ ID NO: 2; or said composition further comprising an IFN antagonist.

Election by Original Presentation

Newly submitted claims 87 and 92 are directed to inventions that are independent or distinct from the invention originally claimed for the following reasons: The composition claims previously presented and examined included the mutant polypeptide of claim 62 optionally comprising an IFN antagonist. New claims 87 and 92 encompass non-elected subject matter, and are directed to a composition comprising the polypeptide of claim 62, further comprising IFNβ, and covalently linked IFNβ.

Thus, claims 87 and 92 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim.

Claims 62, 66-71, 75-82, 88, 89, 93 and 94 are under current examination.

Response to Nucleotide and /or Amino Acid Sequence Disclosures 37CFR§1.821-1.825

Applicant has amended the legend of Figure 2 to refer to SEQ ID NO: 1. in the paper filed 9/28/2006. The specification is therefore in compliance with 37 CFR§1.821 (d).

Response to Claim Objections

Claims 62 and 75 were previously objected to in the office action dated July 26, 2006 based on formal matters. In view of Applicant's amendment of claim 62 correcting a typographical error and amendment of claim 75 to correctly refer to preceding claim numbers, the claim objections are hereby withdrawn.

New Claim Objections

Claims 88 and 89 are newly objected to because of the following informalities: the claims have not been amended to recite the elected species of the invention, multiple sclerosis as an autoimmune disease; and encompasses non-elected subject matter, i.e. cancer, viral disease and a broad variety of autoimmune diseases. Appropriate correction is required.

Response to Claim Rejections - 35 USC § 112, Written Description

Claims 62, 67-71, 75-83 and 85 were rejected under 35 U.S.C. §112, first paragraph, in the office action of July 26, 2006, as failing to comply with the written description requirement. Applicant's cancellation of claims 83 and 85 renders their rejection moot. In view of Applicant's arguments and amendment of claim 62 indicating that the claim is directed to an isolated IFNAR2 polypeptide comprising the sequence of SEQ ID NO: 2, the previous rejection is hereby withdrawn.

Response to Claim Rejections - 35 USC § 112-Scope of Enablement

Applicant's claim amendments have necessitated the following new grounds of rejection.

Claims 62, 66-71, and 75-82 stand rejected under 35 U.S.C. §112, first paragraph, for lacking an enablement for the full scope of the invention. The rejection set forth on pp. 6-7 of the

office action dated July 26, 2006 is maintained for claims 62, 66-71, and 75-82 and further applied to new claim 93, for reasons of record.

Applicants disagree with the rejection and state that the prior art teaches that each of the alternative IFNAR2 alternative splice variants bind IFNβ through the extracellular domain, and that the claimed genus, comprising polypeptides comprising the sequence of SEQ ID NO: 2 wherein alanine substitutions at positions 78 (histidine) and 100 (asparagine) result in synergistic binding to TGFβ, can be created and identified without undue experimentation by one of ordinary skill in the art using standard mutagenesis techniques, and assayed as described in the specification. Further arguing, that one of ordinary skill in the art understands that protein domains are to a large extent independent in terms of their structure, function and folding behavior. This is particularly the case for extracellular protein domains, which one of ordinary skill in the art understands may properly be conceptualized as distinct folding units.

Applicant's arguments have been fully considered, but are not found persuasive. Applicants attention is again drawn to page 1, paragrpah [0003] of the their amended specification that states: type I interferons include interferon α, interferon β and interferon ω, while type II interferon includes interferon γ. IFNAR 2 is the beta subunit or beta chain of the type I IFN receptors (p. 2, paragraph [0006], and as the polypeptide claimed in claim 62 comprises the sequence of SEQ ID NO: 2, other type I IFN receptors cannot be excluded, and hence encompass isolated and mutated polypeptide sequences of numerous receptor variants of the type I IFN receptors, such as membrane bound, cytoplasmic or soluble forms. Applicant's reference to TGFβ binding is unclear, as IFNAR2 is an interferon receptor

Moreover, the claims allow for the addition of any of numerous amino acid to various regions of SEQ ID NO: 2 that can introduce substantial variation, affecting binding of IFNβ. Applicant's argument that protein domains are to a large extent independent in terms of their structure, function and folding behavior is contrary to the teachings of the prior art. For example, Bowie, et al. (Science, 247: 1306-10, 1990) provide notable insight into the lack of reasonable predictability for the mutation of any particular protein. Bowie state that while many substitutions may be tolerated, in other cases substitutions may not be tolerated at all (e.g., 1306, col. 2, paragraph 2). Moreover, the significance of surface and buried amino acids while is not

reasonably predictable either (pp. 1306-07), surface sites may not have any importance, but sometimes they are absolutely important due to binding (p. 1308), and predicting structure with reasonable predictability is generally limited to homologous proteins, but even that is difficult due to alignment problems (p. 1308). Bowie continues: it is not reasonably predictable that any particular amino acid change, deletion, or addition would provide a functional molecule with similar activity, and only painstaking analysis would provide such information for any particular change (e.g., pp. 1309-10). These observations have been further supported by the findings of Skolnick et al. (TIBTECH 18:34-39, 2000), stating: "Knowing a protein's structure does not necessarily tell you its function" (Box 2, p. 36), noting that "alternatives are needed to assign the biochemical function of the 30-50% of proteins whose function cannot be assigned by any current methods" (second column, p. 37). Therefore, it remains unknown whether the mutations of his 78 and asp 100 in SEQ ID NO: 2 would retain their synergistic increase in binding IFNβ, following a fusion to any of numerous unknown amino acid sequences of unlimited size, that can introduce substantial variation, affecting binding of IFNβ.

Therefore, it is maintained that the specification is only enabling for an isolated human IFNAR2- EC polypeptide, wherein amino acid residues His 78 and Asp 100 of the extracellular domain are substituted by alanine, as set forth in SEQ ID NO: 2.

Response to Claim Rejections - 35 USC § 112-Lack of Enablement

Applicants' claim amendments have necessitated the following new grounds of rejection.

Claims 83 and 85 stand rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Applicant's cancellation of claims 83 and 85 renders their rejection moot. The ground of rejection set forth on pp. 7-8 of the previous office action dated July 26, 2006 is applied to new claims 88, 89 and 94 for reasons of record.

Applicant disagrees with the rejection, arguing that a simulation of the concentration of bound and free IFNβ in the presence of different concentrations of mutated IFNAR2 based on the law of mass action and a Kd of 3nM (tested by reflectometric interference spectroscopy) is provided in Figure 1. The simulation demonstrates that in order to achieve 20% free IFNβ (10 pM or 100 Units) and 80% bound, only about 0.24 nM of the mutated IFNAR2 polypeptide is

required compared to 12.5 nM of wild type IFNAR2; and that the essential accuracy of the simulation depicted in Figure 1 is verified in Example 7. Further arguing, a "therapeutically effective" amount of a composition comprising mutated IFNAR2 polypeptide, according to the specification, is one which results in modulation of the biological activity of IFNβ, for example by enhancing its stability, enhancing its potency, or prolonging its in vivo effects. As the specification makes clear, that result is optimally obtained at concentrations of 0.24 nM-0.4 nM of mutated IFNAR2 polypeptide, and that one of ordinary skill in the art understands that compositions of the instant invention are effective for treating any disease that responds to modulation of bioavailable IFNβ. For example, intrathecal administration of IFNβ has been demonstrated to be effective in reducing the symptoms of multiple sclerosis (MS). Regarding claim 94, Applicant refers to paragraph [0063] of the specification, stating mutated IFNAR2 polypeptide can act as a carrier molecule for an antagonist of the IFN receptor, so long as the antagonist binds the mutated IFNAR2 receptor and has antagonistic activity on the IFN receptor; and selecting a "therapeutically effective" amount of a composition comprising mutated IFNAR2 polypeptide and an antagonist is well within the skill of the ordinary artisan and may be determined without undue experimentation, as one of ordinary skill in the art can easily determine the affinity of the antagonist for the mutated receptor and use the laws of mass action to determine a therapeutically effective concentration of IFNAR2 receptor and antagonist.

Applicant's argument has been fully considered, but not found to be persuasive. It is noted that Example 7 is directed to assessment of anti-viral activity and not multiple sclerosis as an autoimmune disease. Further, as was indicated on page 9 of the first office action, the prior art teaches that the role and contribution of IFNAR2, to ligand binding and signal transduction remains unknown, and that soluble IFNAR2a has been found to inhibit the functional activity of type I interferon. Further, the instant specification discloses that the advantages of using mutated IFNAR2EC are that it is possible to administer lower quantities of the receptor as a carrier and because of the stabilizing activity of the mutant, it is possible to reduce the amount of IFNβ administered. However, the specification also teaches that "in some inflammatory disorders, where it may be required to lower the IFN concentrations, it is possible under certain conditions to use this mutant as an effective antagonist specifically toward IFNβ" (p. 9, paragraph 0035).

Thus, it remains unknown whether an administered amount of an IFNAR2 mutant polypeptide would act as a protagonist or antagonist of IFNβ in treating multiple sclerosis. The specification also fails to provide a description of what constitutes a therapeutically effective amount of a composition comprising the IFNAR2 mutated polypeptide and an IFN antagonist, as recited in claims 93, and how an Artisan would differentiate between said therapeutic amount serving as a carrier for IFN versus an antagonist for IFN.

Applicant's reference to paragraph [0063] of the specification fails to address a number of issues raised by the proposed binding of an antagonist to the mutated IFNAR2 receptor, such as determining whether the binding of any of numerous unknown and yet to be discovered molecules can simultaneously bind to the mutated receptor and at the same time exhibit a therapeutically effective antagonistic activity against IFNβ to treat an autoimmune disease and counter the potential protagonist effects of the IFNAR2 polypeptide. However, "case law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not to find out how to use it for themselves." *In re Gardner* 166 USPQ 138 (CCPA) 1970.

The specification also fails to provide any description wherein said composition has been administered to a patient having an autoimmune disorder or multiple sclerosis, either alone or in combination with IFN. Therefore, the reference to "therapeutic amount" is in context of the different properties (i.e. as protagonist and antagonist) attributable to an IFNAR2 mutant polypeptide. Applicants have failed to address the issues set forth in the final office action, regarding the combined administration of the receptor and an IFN antagonist, in the context of their different properties as protagonist and antagonist.

Thus, the previous ground of rejection is applied to new claims 88, 89 and 94 is for reasons of record and the discussion set forth above.

Response to Claim Rejections - 35 USC § 103

Claims 62, 66-71 and 75-76 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Piehler et al. (of record). The rejection set forth on pp. 8-9 of the office action

dated July 26, 2006 and the Advisory action dated October 17, 2006 is maintained for claims 62, 66-71, and 75-76 for reasons of record.

Applicant disagrees with the rejection, stating that the Examiner has failed to consider evidence of secondary considerations, such as unexpected results. Specifically, that the claimed double mutants cause a synergistic effect on the affinity of the polypeptide to IFNβ compared to a single mutations at positions H78 and N100, that is factual evidence and does not constitute attorney argument, and that Piehler fails to teach or suggest such a result. Applicant further argues that Piehler, not only fails to teach or suggest any synergistic effect of a double mutation on IFNAR2 affinity for TGFβ, Piehler actually teaches that such a result is unexpected, because according to Piehler, substituting alanine for histidine at position 78 (H78A) and asparagine at position 100 (N 100A) of IFNAR2 decreases the dissociation rate constant for IFNβ by almost twofold and fourfold respectively. The change in the free energy of binding IFNβ is disclosed as -1.9 kJ/mole for H78A and -3.1 kJ/mole for N100A. According to Piehler, and as is known in the art, the change in free energy for a multiple mutant should equal the sum of energy changes of the individual single mutations. Thus, for the claimed double mutant H78A/N100A, a change in free energy of binding IFNβ of 5.0 kJ/mole is the expected result. According to the formula (5) of Piehler, this corresponds to an expected 8-fold increase in affinity of H78A/N 100A for IFNβ. The present specification, however, teaches that H78A/N 100A exhibits a greater than 50-fold increase in affinity - more than six-times the expected result. Applicant points out to the Examiner that the calculated 8-fold increase in affinity of H78A/N100A is based on sound scientific principles of fact and does not constitute, mere attorney argument, further citing *In re Soni*, that where the evidence relied upon by Applicant to show unexpected results is in the specification to which Applicant has attested, a declaration according to 37 C.F.R. § 1.132 is unnecessary.

Applicant's arguments have been fully considered, but are not found persuasive. Moreover, as was indicated on p. 11 of the previous office action, Piehler et al. specifically describe the mutant H78A as stabilizing the complex with IFN-β nearly two fold; the mutation N100A decreasing dissociation rate constant for IFNβ by almost fourfold; and further stating: "It would be interesting to explore the phenotype of a H78, N100 double mutation in ifnar2, which

should have about a 20-fold tighter binding for IFNβ". Thus, Piehler expected a synergistic effect for the double mutation. Regarding, the expected free energy calculations, the correlation of thermodynamics with activity is not a one to one relationship, and cannot be accurately predicted. Piehler specifically state that it would be interesting to explore the phenotype of a H78, N100 double mutation in ifnar2. If the outcome of the double mutation could be accurately predicted, it would not be "interesting" to explore such a result. When the teachings of Piehler are considered in total, there is no basis for predicting an absence of synergy between the two mutations in increasing the affinity of the ifnar2 receptor for IFNbeta. As stated in MPEP 716.02(c)II. >< EXPECTED BENEFICIAL RESULTS ARE EVIDENCE OF OBVIOUSNESS; "Expected beneficial results are evidence of obviousness of a claimed invention, just as unexpected results are evidence of unobviousness thereof." *In re Gershon*, 372 F.2d535, 538, 152 USPQ 602, 604 (CCPA 1967); *Ex parte Blanc*, 13USPQ2d 1383 (Bd. Pat. App. & Inter. 1989). The instant claims are directed to an isolated human IFNAR2 polypeptide characterized by H78A and N100 A double mutations. Piehler explicitly provides the motivation to make such a double mutant.

Therefore, the rejection of claims 62, 66-71 and 75-76 is maintained for reasons of record and the foregoing discussion.

Claims 77-81 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Piehler et al. (of record), in view of Campbell et al. (of record). The rejection set forth on pp. 8-9 of the office action dated July 26, 2006 is maintained for claims 77-81 and further applied to amended claim 82, for reasons of record.

Applicant disagrees with the rejection, citing the deficiency of Piehler et al. indicated for claims 62, 66-71 and 75-76 above. Such is not found persuasive, in view of reasons of record and the discussion set forth above. Therefore, the rejection of claims 77-81 is maintained and further applied to amended claim 82, as claim 82 no longer recites the limitation of an IFN antagonist.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00-4:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on **(571) 272-0739**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

For all other customer support, please call the USPTO Call Center (UCC) at **(800) 786-9199**.

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